Title: Increased cortical volume revealed by atlas-based volumetry in a bigenic mouse model of Alzheimer's Disease

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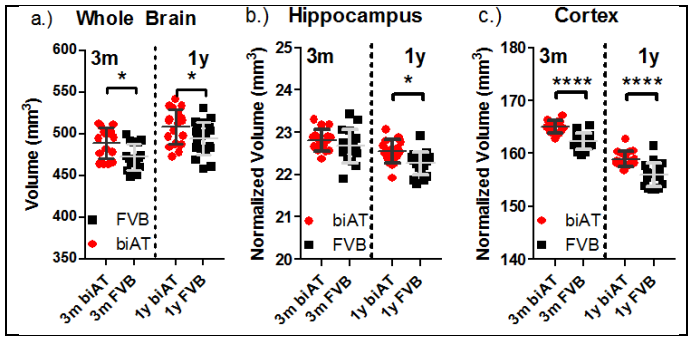
Introduction: Despite atrophy being an established MRI biomarker in Alzheimer's Disease (AD) patients (1), clear atrophy cannot always be detected in amyloid models (2, 3, 4). We make use of the biAT model, combining APP and tau pathology and displaying an early behavioral phenotype representing prodromal AD (6). We made use of atlas-based registration and voxel-based morphometry(VBM) on *in vivo* anatomical mouse MRI data to investigate regional volume changes in the biAT model.

Methods:
MRI: APP.V717I x Tau.P301L (biAT) and FVB control mice were imaged at 3 (biAT: 16, FVB: 16) and 12 (biAT: 18, FVB: 19) months of age. Imaging was performed on a 9.4T small animal MRI (Bruker). 3D T_2-weighted MRI images were acquired (TR/TE:1000/36ms, resolution 90µm isotropic).
Processing: After bias field correction and intensity normalization using in-house developed Matlab scripts (The Mathworks) (7), data processing was performed using a nonrigid registration protocol incorporating NiftyReg. The reference image was a study-specific 3-month old FVB template. VBM was performed on the Jacobian maps in template space using SPM, and thresholded for a family-wise error rate of 5%. Regional volumes were normalized to a brain volume of 500µl.



Results: biAT animals displayed increased whole brain volume at 3 and 12 months *vs*. FVB (3m: 489 ± 17 vs. 472 ± 15 mm^3, p=0.011, 1y: 508 ± 20 *vs*. 494 ± 19 mm^3, p=0.038). VBM revealed that these volume differences are largely localized to the region of the frontal cortex and basal ganglia. Regional volumes normalized for brain volume revealed subtle but highly significant increases in volumes for the cerebral cortex of biAT mice vs FVB (3mo: 165.0 *vs.* 162.3mm^3, 1yo: 158.9 *vs*. 155.9 mm^3, biAT *vs.* FVBy; p<0.0001). We did not observe reduced hippocampal volume, although a minor increase in normalized volume was found at 12mo (22.6 *vs*. 22.3, p<0.05.).

Conclusions: With our methods, we were able to reproducibly resolve very small volume differences. Increased cortical size is not an unprecedented finding in AD models, where results are often contradictory or negative (2,3,4). The volume increases we report are the result of a secondary mechanism, most likely gliosis and/or edema.

References: 1. Jack et al., Lancet Neurol. 2010, 2. Hébert et al., Neurobiol. Aging 2013, 3. Lau et al., Neuroimage 2008, 4. Maheswaran et al., Brain Res. 2009, 5. Yang et al., Neuroimage 2010, 6. Terwel et al., Am J. Pathol. 2008, 7. Vande Velde et al., Neuroimage 2012

Abstract category:

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